

1 REMARKS

2 Status of the Claims

3 Claims 1-19 and 28 are pending in the present application, Claims 20-27 having been canceled
4 herein as being directed to a non-elected invention (subject to applicants' right to file a divisional
5 application during the pendency of the present application), and new Claim 28 having been added.
6 Claims 1, 7, 13, 15, 18 and 19 have been amended to more clearly defined the invention.

7 Amendment of the Specification

8 Applicants have amended the specification in two different manners. First, inadvertent errors
9 dealing with grammar and the title of a patent application identified by its U.S. serial number have been
10 corrected. Second, material from a commonly assigned and co-pending U.S. patent application, which
11 was specifically incorporated by reference in the application as filed, has been added to the specification.
12 Neither amendment represents the addition of any new matter.

13 The material which had been incorporated by reference has been added to provide additional
14 written description related to a specific type of reactor. As discussed in detail below, applicants have
15 amended the independent claims to further define the type of reactor employed in the present invention.
16 As amended, the claims now define an apparatus comprising a reactor configured to be operated
17 continuously, such that a volume of product produced by the reactor is a function of the flow rate of the
18 reactants introduced into the reactor, and a length of time during which such reactants are introduced into
19 the reactor. Significantly, it should be recognized that the flow rate of reactants into a batch reactor is
20 largely irrelevant, as once introduced into the reactor the reactants are held for whatever period of time is
21 required to complete the batch process. In contrast, controlling the flow rate of reactants into a continuous
22 process reactor is critical in enabling control of reaction times to be achieved. For example, reactions
23 requiring relatively little reaction times can be implemented using a relatively higher flow rate, while
24 reactions requiring relatively longer reaction times must be implemented using relatively slower flow
25 rates.

26 As originally filed, the application provides a written description of a continuous flow reactor (a
27 type of reactor which is distinguishable over a batch reactor) in the following sections: The paragraph
28 beginning on line 16 of page 4 (which discloses using a pump to achieve a desired flow rate through the
29 reactor), the first paragraph of page 11 (which discusses the importance of flow rates), the second
30 complete paragraph of page 12 (which again discusses the importance of flow rates), the last paragraph on

1 page 14 (which discusses flow rates and how a residence time chamber can be used to extend the reaction
2 time), the first full paragraph of page 17 (which describes the continuous flow of reactants and solvent
3 through the reactor), the second full paragraph of page 19 (which describes the continuous flow of
4 reactants and solvent through the reactor in the context of FIGURE 4), and the final paragraph on page 28
5 (which discloses using relatively fast flow rates for reactions requiring relatively short reaction times, and
6 using relatively slow flow rates for reactions requiring relatively long reaction times).

7 The previously incorporated by reference material which has been added to the specification by
8 the present amendment provides additional written description of a preferred stack plate reactor
9 configured for continuous operation (as opposed to batch operation). Significantly, the added material
10 provides a detailed description of the movement of reactants and product through the preferred stack plate
11 reactor, illustrating the continuous flow of material through the preferred reactor.

12 Claims Rejected under 35 U.S.C § 112, Second Paragraph

13 The Examiner has rejected Claims 7, 8, and 19 under 35 U.S.C § 112, second paragraph, as being
14 indefinite for failing to particularly point out and distinctly claim the subject matter which applicants
15 regard as the invention. Specifically, the Examiner asserts that the phrase “heat exchanger being coupled
16 in fluid communication with the reaction module” is unclear, because the exchangers transfer energy from
17 one fluid to another fluid without mixing the two.

18 Applicants have amended Claims 7 and 19; thereby obviating the indefiniteness rejection.
19 Accordingly, the rejection of Claims 7, 8, and 19 under 35 U.S.C § 112, second paragraph, should be
20 withdrawn.

21 Claims Rejected under 35 U.S.C § 103

22 The Examiner has rejected Claims 1-6, 9, 11-16, and 18 under 35 U.S.C § 103(a) as being
23 obvious over Rosenberg (WO009300625). The Examiner admits that Rosenberg does not teach each
24 element recited in applicants’ claims, but asserts that it would have been obvious to one of ordinary skill
25 in the art to modify Rosenberg’s apparatus to achieve an equivalent invention. Applicants respectfully
26 disagree for the following reasons

27 Referring to Claim 1, applicants have amended Claim 1 to further define the reactor. As
28 amended, the reactor defined in Claim 1 is configured to *operate continuously over a period of time, such*
29 *that a volume of a desired product produced by the reactor is a function of both a flow rate associated*
30 *with the plurality of reactants introduced into the reactor, and a length of time during which the plurality*

1 *of reactants are continuously introduced into the general purpose reactor, as opposed to a volume of a*
2 *reactor operating in a batch mode.*

3 The reactor disclosed by Rosenberg is specifically configured to operate in a batch mode, and
4 there is no evidence to conclude that it would have been obvious to one of ordinary skill in the art at the
5 time of the invention to replace the batch reactor disclosed by Rosenberg with a continuous reactor as
6 recited in Claim 1. Significantly, there is no evidence that an artisan of ordinary skill would have
7 recognized any benefit that could be achieved by making such a substitution, nor is it evident that such a
8 substitution would solve any problem that had been recognized by the art.

9 Applicants believe that prior art sequential reaction systems have heretofore been implemented
10 using batch reaction vessels, as opposed to a reactor configured for continuous operation. In a batch
11 process, specific volumes of reactants are introduced into a finite reaction volume. If the reaction volume
12 is 50 milliliters, then only 50 milliliters of product can be produced per batch (i.e., before the reactor is
13 emptied, cleaned for reuse, and additional reactants are introduced). In contrast, a reactor configured for
14 continuous operation will continuously receive reactants and discharge a product, such that the volume of
15 product produced is a function of the flow rate of the reactants introduced into the reactor, and a length of
16 time that reactant flow rate is maintained. The volume of product produced in a continual flow reactor *is*
17 *not* a function of the size of the reactor volume.

18 The reaction chamber of Rosenberg is a typical batch reaction vessel, because it contains a "solid
19 support" (for example, see page 4, lines 14-15; and page 17, lines 26-36 of Rosenberg's disclosure). Such
20 solid supports are used in reactions that are characterized by including a first step in which a first reactant
21 is attached to the solid support, a second step in which a second reactant is introduced to react with the
22 first reactant bound to the solid support, and a final step in which the resulting product is released from
23 the solid support. Thus, the volume of the product produced in the reactor is a function of the volume of
24 the first reactant bound to the solid support. Rosenberg teaches that the coupling reaction is performed by
25 cycling the amino acids through the reaction chamber where the first reactant is bound to the solid support
26 as many times as required to complete desired coupling reaction (for example, see the second paragraph
27 on page 24 of Rosenberg's disclosure). The cycling disclosed by Rosenberg is significantly different than
28 the operation of a continuous flow reactor, where reactants are introduced into a reactor and a product
29 exits the reactor in a continuous fashion as a function of a flow rate used to introduce the reactants into the
30 reactor. Significantly, reactors configured to operate continuously generally include one or more internal

1 volumes in which one or more reactants are mixed. No solid support is required to initiate the reaction.
2 Thus, reactants and product can continually flow through the internal volumes of the reactor in a
3 continuous process, rather than batch process. A preferred microreactor comprising a plurality of stacked
4 plates and internal reaction volumes is described in the amended specification. The specification, both as
5 amended and as originally filed, clearly describes operation of a reactor such that reactants are
6 continuously introduced into a reactor, and a product is continuously collected from the reactor.

7 Significantly, the reaction time in a batch vessel is determined by the length of time the reactants
8 are held within the reaction vessel. The reactor is ready for use again only after completely removing the
9 reaction mixture and cleaning the reaction vessel to prepare it for reuse. Thus, a series of steps are
10 required for performing one single reaction. Rosenberg describes a technically complicated delivery
11 method (pressure/negative pressure, vacuum, etc.), as well a a cleaning cycle that occurs each time the
12 reactor is used to process a batch.

13 In contrary, the reaction time in a reactor configured for continuous operation is determined by the
14 interior volume of the reactor, the flow rate of the reactants to the reactor, and a length of time the flow
15 rate is maintained. Thus, a volume of product significantly larger than the interior volume of the reactor
16 can be produced, simply by maintaining a continuous flow rate through the reactor over a period of time
17 required to achieve the desired production volume.

18 The use of a continuous flow reactor in place of a batch reactor enables numerous benefits to be
19 achieved, benefits which do not appear to be recognized by the prior art. By using a spacer liquid to
20 separate sequential reaction products (see FIGURE 4 of the specification as filed, with *S* representing a
21 spacer liquid or solvent), it is possible to continuously perform a plurality of sequential syntheses using
22 only a single reactor. While Rosenberg also implements a single reactor, the use of a continuous flow
23 reactor in place of a batch reactor enables the following benefits to be obtained:

- 24 • *The amount of product is not determined by the inner volume of the reactor; the volume of*
25 *the product can exceed or fall below the reactor volume, depending on flow rate and time.*
- 26 • *A relatively large library can be produced within a relatively short time using only a*
27 *single reactor (because many of the cleaning steps required by Rosenberg are not*
28 *required to use the reactor system of the present invention, total time to produce the*
29 *desired library is significantly reduced).*

- 1 • *At any one time there can be more than one different product moving through the entire*
2 *system. Referring to FIGURE 4, as the last of product of A1B1 is being directed into a*
3 *product collector, solvent used to flush the reactor is exiting the reactor, and reagents A1*
4 *and B2 are beginning to enter the reactor, to produce the product of A1B2. This feature*
5 *leads to significantly shorter cycle times, as the cleaning cycle can be started during the*
6 *reaction process, and not after the reaction process is completed.*
- 7 • *Downtime (i.e., the amount of time the reactor cannot be used to produce a product)*
8 *required for cleaning is a function of the number of different chemical products being*
9 *produced (i.e., A1B1, A1B2, etc, generally as indicated in FIGURE 4), not the number of*
10 *different batches being produced. If Rosenberg's system is used to generate five batches*
11 *of A1B1 and four batches of A1B2, then nine cleaning cycles will be required. Applicants'*
12 *system can generate the same volume of A1B1 and A1B2 using only two cleaning cycles,*
13 *meaning the reactor is available to be online producing product for a greater amount of*
14 *time.*

15 The prior art simply does not teach or suggest any of the above-identified benefits. Thus, it
16 appears that modifying Rosenberg's system to include a reactor configured for continuous processing
17 requires an impermissible application of hindsight. Claim 15 has been similarly amended to recite a
18 reactor configured for continuous operation. Furthermore, the language of Claim 15 has been amended to
19 define the controller as manipulating the flow rates of the reactants to accommodate different reaction
20 times for different reactions, the controller establishing a relatively higher flow rate for reactions requiring
21 a relatively shorter reaction time, and the controller establishing a relatively slower flow rate for reactions
22 requiring a relatively longer reaction time. Such a controller is not disclosed or suggested by Rosenberg.
23 It is well recognized that the pending claims must be patentable for at least the same reasons as the claims
24 upon which they depend. Accordingly, the rejection of Claims 1-6, 9, 11-16, and 18 under
25 35 U.S.C § 103(a) as being obvious over Rosenberg should be withdrawn.

26 Referring to Claims 6 and 18, the Examiner has admitted that Rosenberg does not specifically
27 teach a detector located between the reaction chamber and the output valve. The Examiner has asserted
28 that the incorporation of such a detector would have been obvious to one of ordinary skill in the art in
29 order to control the process of product formation. Applicants respectfully disagree.
30

1 Significantly, the automatic detector defined by applicants is configured to provide *an output*
2 *signal to the system controller that is indicative of whether a spent solvent or a desired chemical product*
3 *is flowing from the reaction module* (Claim 18 uses slightly different language, but parsing Claim 18
4 makes it clear that the detector must be capable of distinguishing a solvent from a product). If an artisan
5 of ordinary skill was motivated to modify Rosenberg's synthesis system to control the process of product
6 formation, there is no evidence that such an artisan would have been motivated to add a detector
7 specifically configured to distinguish between a reaction product and a spent solvent. Rosenberg's
8 apparatus is particularly well-suited to synthesize oligomers. The Examiner appears to argue that an
9 artisan of ordinary skill would have been motivated to modify Rosenberg's apparatus to include a detector
10 configured to detect oligomers. Such a detector is not equivalent to a detector configured to provide an
11 output signal indicative of whether a spent solvent or a desired chemical product is flowing from the
12 reaction module. Claims 6 and 18 are distinguishable over the cited art for this additional reason.

13 With respect to Claims 10 and 17, the Examiner admits that Rosenberg does not disclose a
14 residence time chamber, and argues that it would have been obvious to one of ordinary skill in the art to
15 incorporate residence time chambers such as those disclosed by Joslyn into Rosenberg's apparatus, to
16 achieve an equivalent invention. As discussed in detail above, Rosenberg describes a batch reactor.
17 Residence time chambers are uniquely suited for use with reactors configured for continuous processing,
18 not batch processing. As discussed in detail above, it appears to require an impermissible application of
19 hindsight to replace the batch reactor disclosed by Rosenberg with a continual process reactor as defined
20 and recited in applicants' claims. Such an application of hindsight would appear to be similarly required
21 to modify Rosenberg to incorporate a residence time chamber. For this additional reason, Claims 10 and
22 17 are distinguishable over the cited art.

23 Claim 13 has been amended to specifically define the outlet valve as comprising *a proportional*
24 *valve configured to act as a throttle to enable a pressure along a reaction path to be selectively varied*.
25 The specification as filed clearly refers such an embodiment (see page 15, second paragraph). Rosenberg
26 discloses a pressure source (such as an argon cylinder) being included to enable pressure conditions to be
27 varied. However, the pressurized gas supply disclosed by Rosenberg is not equivalent to a proportional
28 valve being disposed in between a reactor and an automated product collector. It appears such a
29 modification would require an impermissible use of hindsight. Claim 13 is therefore distinguishable over
30 the cited art for this additional reason.


1 Patentability of Newly Added Claims

2 Newly added Claim 28 is based on Claim 1 as originally filed, with the incorporation of the
3 additional elements of the detector of Claim 6 and a controller configured to analyze the output signal
4 provided by the detector to selectively actuate the output valve to either *couple the reaction module in*
5 *fluid communication with the automated product collector* or to *couple the reaction module in fluid*
6 *communication with the spent solvent reservoir*.

7 As discussed in detail above, a detector configured to distinguish between a solvent and a product
8 does not appear to be reasonably disclosed by the cited art, nor does the cited art appear to support the
9 conclusion that it would have been obvious to modify Rosenberg's system to include such an element.
10 Even if, as the Examiner suggests, one of ordinary skill in the art would have been motivated to modify
11 Rosenberg's apparatus to include some sort of detector, there is no evidence that such an artisan would
12 have selected a detector configured to distinguish between a solvent and a product, or to configure the
13 controller to selectively actuate the output valve as noted above. It appears such a modification would
14 require an impermissible use of hindsight. Claim 28 is therefore distinguishable over the cited art.

15 Accordingly, all of the claims now submitted define patentable subject matter that is neither
16 anticipated nor obvious in view of the prior art cited. The Examiner is thus requested to issue the present
17 patent in view of the amendments and the remarks submitted above. If there are any questions that might
18 be addressed by a telephone interview, the Examiner is invited to telephone the undersigned attorney, at
19 the number listed below.

20
21 Respectfully submitted,

22 
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27 MAILING CERTIFICATE

28 I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed
29 envelope as first class mail with postage thereon fully prepaid addressed to: Commissioner for Patents, Alexandria,
30 VA 22313-1450, on April 4, 2006.

Date: April 4, 2006

